The attached information was received by FDA from the Office of Management and Budget. This information was received by OMB at a meeting with the attendees on the list enclosed. This meeting was held on July 28, 1998. OMB staff have stated that the meeting was held in accordance with the guidelines specified in Executive Order 12866.

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7/28/98	Name	Organization	Number
	Wendy Taylor	OMB	202/395-7216
	Reid Detchon	Podesta Assoc	202/393-1010
	Walter Moore	Genentech	202/296-7272
	Steve Lawton	Hogan & Hartson	202/637-8615
	Allen Goldhammer	BIO	202/776/0603
	Robert Brady	Hogan & Hartson	202/637-6969
	Tony Podesta	Podesta Assoc	202-393-1010
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	Dan Arbeit	OMB/OIRA	395-3852

Changes Necessary to Conform Proposed Regulations on Dissemination of Information on Off-Label Use to Congressional Intent

1. Definition of "Clinical Investigation" and "Scientifically Sound" Determination. The law authorizes distribution of scientific articles, peer reviewed by experts, "about a clinical investigation . . . which would be considered to be scientifically sound *by such experts*". Instead of relying on peer review as the basis for insuring quality and accuracy, the proposed regulations would significantly restrict scientific articles and reference publications eligible for dissemination in two ways. First, the proposal crafts a narrow definition of "clinical investigation", which restricts "clinical investigations" to those that are prospectively planned. Second, the proposed regulation would authorize *FDA* to determine whether the clinical investigations described in articles are "scientifically sound". Congress intended that a scientific journal's peer reviewers, and not FDA, be the judge of scientific soundness.

The definition of "clinical investigation" should be deleted from the proposal. In addition, the entire concept of FDA review of whether a clinical investigation is scientifically sound must be deleted.

2. "Economically Prohibitive" Exception. The law requires that a manufacturer who seeks to disseminate information about a new use either certify that it has filed (or within 6 months will file) a supplemental NDA/BLA for the new use, or will submit a proposed protocol and schedule for conducting studies

necessary to do so. The law authorizes an exception to these requirements if the Secretary determines that it would be economically prohibitive to incur the costs necessary for the submission of a supplemental application. The law *requires* FDA to consider (in addition to other considerations it may find appropriate) the lack of availability of exclusive marketing rights for the drug and the size of the patient population expected to benefit from the approval of the supplement.

The proposed regulation ignores the mandate to consider the two factors specified in the statute and instead makes the "economically prohibitive" exception available only in the case in which the estimated cost of studies of the *new use* exceeds the estimated *total revenue* from the drug (less expenses). Enormously detailed information about pricing and market share would be required to be submitted. The final regulations should dispense with the entire concept of requiring that estimates of economic benefit to the manufacturer from all sales of the drug be less than the costs of studies of the new use. In its place, FDA should establish a simple, bright line test, based on the two statutory criteria, specifying that (1) no market exclusivity resulting from patents, orphan drug exclusivity or Waxman-Hatch statutory exclusivity provisions are available for the medical product that is the subject of the scientific publication or (2) the patient population likely to be served by the new indication will not exceed an established number, such as 100,000.

3. <u>"Ethical" Exception</u>. The law likewise authorizes an exemption from the supplement/protocol requirements on the basis that it would be unethical

to conduct the studies necessary for the supplemental application. The law *requires* the FDA, in determining whether such studies would be unethical, to consider whether the new use involved is the standard of care. Detailed language in the conference report spells out circumstances that may be used by FDA in making its determination as to whether the new use represents the standard of care; examples include inclusion in specified compendia or practice guidelines. The law also suggests consideration of whether the new use involves a combination of products involving more than one sponsor. But the proposed regulations would limit application of the exemption to situations in which withholding the drug in the course of a clinical trial would present an unreasonable risk of harm to patients. Again, in the interests of creating only a very narrow exemption, FDA has ignored Congressional intent.

The final regulations should establish a bright line to be applied by FDA in determining whether to grant an exemption on ethical grounds. The bright line test should be (1) that the new use represents the standard of care, as represented by inclusion in specified compendia or practice guidelines; or (2) the new use involves a combination of products of more than one sponsor. FDA should grant exceptions on other grounds on a case-by-case basis.

4. 60 Day Review Period. Despite the fact that the law requires that FDA make a determination on an application to disseminate within 60 days, the proposed regulations contemplate that during the 60 day period FDA could determine that FDA requires more information. In such case, the proposed

regulations impose on FDA no time frames for obtaining additional information and approving/disapproving the application. The final regulations should honor the 60 day requirement by requiring that any judgment as to completeness, as well as the decision to allow or disallow dissemination, be made within the 60 day statutory period.

5. Definition of "New Use". The law applies to dissemination of scientific information on a "new use" of an approved drug, defined as "a use not included in the labeling" of the product. The definition of "new use" in the proposed regulations and its preamble should be narrowed to delete comparative claims for approved indications and claims for subpopulations.